American Journal of Epidemiology
Copyright © 2003 by the Johns Hopkins Bloomberg School of Public Health
All rights reserved

Vol. 157, No. 10
Printed in U.S.A.
DOI: 10.1093/aje/kwg055

Alcohol Concentration and Risk of Oral Cancer in Puerto Rico

Wen-Yi Huang[1], Deborah M. Winn[2], Linda M. Brown[1], Gloria Gridley[1], Eleuterio Bravo-Otero[3], Scott R. Diehl[4], Joseph F. Fraumeni Jr.[1], and Richard B. Hayes[1]

[1] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD.
[2] Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD.
[3] School of Dentistry, University of Puerto Rico, San Juan, Puerto Rico.
[4] New Jersey Dental School, University of Medicine and Dentistry of New Jersey, Newark, NJ.

Received for publication July 11, 2002; accepted for publication November 13, 2002.

Alcohol consumption is a major risk factor for cancers of the mouth and pharynx (oral cancer), but the differential risks by beverage type are unclear. In this 1992–1995 study, the authors examined oral cancer risk in Puerto Rico, comparing alcohol intake among 286 male cases aged 21–79 years and 417 population-based male controls, frequency matched by age. Heavy consumers of liquor (≥43 drinks per week) had strongly increased risks of oral cancer (odds ratio = 6.4, 95% confidence interval: 2.4, 16.8); beer/wine showed only modest effects. Among liquor drinkers, risks were consistently greater for those who drank straight (undiluted) liquor than for those who usually drank mixed (diluted) liquor (odds ratio = 4.0, 95% confidence interval: 2.4, 6.7). Risks associated with combined exposure to tobacco were also more pronounced when subjects drank liquor straight. The elevated risks associated with drinking homemade rum were similar to those for other types of liquor. These results suggest that alcohol concentration is a risk factor for oral cancer independent of the total quantity of alcohol consumed.

alcohol drinking; alcoholic beverages; Hispanic Americans; mouth neoplasms; pharynx

Abbreviations: CI, confidence interval; OR, odds ratio.

Consumption of alcohol in the form of beer, wine, or liquor is a major risk factor for cancers of the oral cavity and pharynx (hereafter referred to as oral cancer) (1–3). On a per-drink basis, the ethanol content of these beverages is similar (10–14 g); however, the liquid volume differs (beer, 3.3 dl; wine, 1.5 dl; and, liquor, 0.4 dl), so alcohol concentration varies by beverage type (beer, 3.4 g/dl; wine, 9.2 g/dl; and straight (undiluted) liquor, 26.7 g/dl) (2). Although liquor is the most concentrated alcoholic beverage, the actual concentration of alcohol in liquor varies depending on whether the drink is consumed straight or is diluted with nonalcoholic mixers. Some have concluded that risks for oral cancer are related to the quantity of alcohol consumed (in grams), irrespective of the concentration, although studies have not addressed in detail the relative contributions of dose versus concentration (4–10).

In a population-based, case-control study conducted in Puerto Rico, we determined usual patterns of liquor consumption as straight versus mixed in addition to collecting detailed quantitative data on beverage types. Oral cancer rates are about two times higher among men in Puerto Rico than among mainland US Hispanics (1, 11), and consumption of straight liquor is common. Furthermore, locally produced, homemade rum is commonly consumed in Puerto Rico and has been suspected to contain potentially carcinogenic contaminants (11). Our study provided a unique opportunity to evaluate the effects of alcohol concentration and the intake of homemade rum as potential explanations for the high rates of oral cancer reported in Puerto Rico.

MATERIALS AND METHODS

Study population

Details of the design of this population-based, case-control study of oral cancer in Puerto Rico are provided elsewhere (1). The present analysis was restricted to men because few

Reprint requests to Dr. Wen-Yi Huang, Division of Cancer Epidemiology and Genetics, National Cancer Institute, EPS 8109, Bethesda, MD 20892-7240 (e-mail: huangw@mail.nih.gov).

women drank substantial quantities of alcohol. Included for study were all Puerto Rican men aged 21–79 years newly diagnosed, between December 1992 and February 1995, with a first, histologically confirmed cancer of the oral cavity (excluding lip and major salivary glands) or pharynx (excluding nasopharynx) (*International Classification of Diseases*, Ninth Revision, codes 141, 143–146, 148, and 149). Cases were ascertained through the Central Cancer Registry of the Department of Health of Puerto Rico and by abstracting patients' medical records. Population controls were selected from among all Puerto Ricans and were frequency matched to cases by age (in 5-year intervals) using a clustered, two-stage area probability method for men younger than age 65 years and a systematic sampling of US Health Care Financing Administration rosters for men aged 65 years or older. The area probability sampling was based on *municipios* (similar to counties) and segments (street blocks of residences or combinations of blocks) for the first and second stages. Three separate samplings from these rosters were made during the course of fieldwork, with approximately one third of the required controls identified during each sampling. Refusal conversion and reinterview procedures were accomplished to ensure high response rates and high-quality interview data, respectively.

A total of 286 male cases and 417 male controls participated in the study, resulting in response rates of approximately 70 percent and 83 percent, respectively, after considering the initial screening process and selected subject refusal. Reasons for nonparticipation included death or illness (81 cases and 12 controls), subject or physician refusal (14 cases and 43 controls), failure to trace (24 cases and 31 controls), and incomplete interview (eight cases).

Interview

Questionnaire data, collected through in-person interviews, were used to assess consumption of alcohol (e.g., ages at which drinking started and stopped, total years of consumption, usual weekday and weekend consumption, beverage types, and usual manner of liquor consumption (straight vs. mixed drinks)), use of tobacco (e.g., ages at which use started and stopped, total years of use, and quantity usually used), usual adult diet, medical and dental history, and demographic characteristics. Beer consumption was assessed as number of 7-, 8-, 10-, or 12-ounce cans or bottles (1 ounce = 0.30 dl); wine consumption as number of 4.0-ounce glasses; and liquor consumption as number of 1.5-ounce shots, 0.2-liter (pint) bottles, or 1.0-liter bottles. Total alcoholic beverage consumption was summed on a per-drink basis (12 ounces of beer, 4.0 ounces of wine, and 1.5 ounces of liquor) from usual weekly intake (combining weekday and weekend amounts) of liquor, wine, and beer and overall. Patterns of liquor intake were characterized as usually taken mixed (i.e., diluted with a nonalcoholic mixer such as water, soda, or fruit juice) or straight (i.e., undiluted). Similar information was obtained separately for consumption of homemade rum.

Men who had consumed fewer than 12 drinks of any type of alcohol in their lifetime or had started and stopped consuming alcohol within 1 year were considered nondrinkers. Men included in the "no tobacco use" category had smoked fewer than 100 cigarettes or had used cigars, pipes, or chewing tobacco for less than 6 months in their lifetime. On the basis of the estimated relative risks for oral cancer (1), we categorized quitting tobacco 10 or more years ago or smoking cigarettes for less than 10 years and using fewer than 10 cigarettes per day as "light tobacco use." Smoking 30 or more cigarettes a day for 30 or more years or smoking cigars or a pipe was considered "heavy tobacco use." Other tobacco-use patterns were categorized as "medium tobacco use."

Written informed consent was obtained from all participants. The study was approved by the institutional review boards at the US National Cancer Institute, Bethesda, Maryland, and the University of Puerto Rico, San Juan.

Statistical analysis

Odds ratios and 95 percent confidence intervals for alcohol consumption were estimated by using unconditional logistic regression (12). In logistic models, consumption of each beverage type and total alcohol intake were divided into four categories (none, >0–<8, 8–<43, and ≥43 drinks per week). All analyses were adjusted for age (<55, 55–59, 60–64, 65–69, 70–74, and 75–79 years), lifetime tobacco use (none, light, medium, and heavy), consumption of raw fruits and vegetables (in quartiles), and educational level (<8 years, 8–11 years, 12 years/high school graduate, and >12 years); these variables were selected because including them singly in the logistic models resulted in changes of 10 percent or more in the odds ratio for alcohol. Adjustment for income did not substantially affect the odds ratio once education was included in the model. Adjustment for residential region (metropolitan San Juan/other) led to essentially no change in the results. Where indicated, risks associated with intake of a specific alcoholic beverage type were adjusted for either other alcohol intake or total alcohol intake. Liquor intake and nonliquor intake as continuous variables were not correlated ($r_{\text{Pearson}} = -0.007$, $p = 0.8$); however, when they were used as categorical variables in the models, there was a modest correlation ($r_{\text{Spearman}} = 0.4$, $p < 0.001$). Statistical trend tests were performed by treating the categorical alcohol variable as continuous in the model, with each level represented by the median value of that category among the controls. All p values were two sided. Men for whom values were missing were excluded from specific analyses.

RESULTS

Cases and controls were similar with respect to age and place of residence, but cases reported less education, lower income, heavier use of tobacco, and less consumption of raw fruits and vegetables (1). Among controls, those who usually drank straight liquor tended to be older, less educated, and heavier smokers compared with liquor consumers who usually drank diluted drinks, drinkers of beer/wine only, and nondrinkers (table 1).

As shown in table 2, after adjustment for potentially confounding factors, the risk of oral cancer was most

TABLE 1. Selected characteristics* of controls (all male) in the oral cancer study, Puerto Rico, 1992–1995

	Liquor drinkers		Drinkers of beer/wine only	Nondrinkers
	Usually drank liquor straight (undiluted)	Usually drank liquor with nonalcoholic mixers		
Controls (no.)	107	163	80	67
Age (years)				
<55	13	28	38	24
55–59	10	16	26	9
60–64	17	19	14	19
65–69	16	18	11	22
70–74	21	12	6	15
75–79	23	7	5	11
Residence				
Metropolitan San Juan	17	33	20	31
Other	83	67	80	69
Educational level				
>12 years	7	31	14	27
12 years/high school	18	19	26	19
8–11 years	12	18	25	11
<8 years	63	32	35	43
Income ($)				
≥20,00	10	22	8	20
15,000–19,999	7	14	22	11
10,000–14,999	32	31	20	26
<10,000	51	33	50	43
Tobacco use†				
None	24	25	37	66
Light	30	37	28	22
Medium	31	27	23	7
Heavy	15	11	12	5
Consumption of raw fruits and vegetables (quartile)				
First	28	26	27	15
Second	23	27	23	27
Third	26	23	24	30
Fourth	23	24	26	28

* Except for numbers of controls, all characteristics are expressed as percentages.

† The four categories are defined in the Interview portion of the Materials and Methods section of the text.

strongly related to heavy liquor consumption (≥43 drinks per week), irrespective of the quantity of beer/wine consumed, while the elevated risks associated with heavy beer/wine consumption were pronounced only among subjects who also consumed moderate to heavy quantities of liquor (≥8 drinks per week). Similar risks were found on a per-drink basis related to weekday and weekend consumption, although greater daily quantities of alcohol were consumed on weekends (data not shown).

Among heavy drinkers, adjusted risks were most strongly related to consumption of liquor (odds ratio = 13.2, 95 percent confidence interval (CI): 6.5, 26.6 after adjustment for consumption of other beverage types; odds ratio = 6.4, 95 percent CI: 2.4, 16.8 after adjustment for total alcohol intake) (table 3). Adjusted risks associated with drinking homemade rum were similar to those for other forms of liquor.

Risks were greater among men who usually drank straight (undiluted) versus mixed (diluted) liquor (odds ratio = 4.0, 95 percent CI: 2.4, 6.7), with consistent patterns of increased risk across most consumption categories (table 4). Risks associated with concentration (i.e., straight vs. mixed) also

TABLE 2. Oral cancer risks associated with consumption of beer/wine and liquor, Puerto Rico, 1992–1995

Liquor (drinks/week)	Beer/wine (drinks/week)											
	Nondrinker			>0–<8			8–<43			≥43		
	No.*	OR†,‡	95% CI†	No.	OR‡	95% CI	No.	OR‡	95% CI	No.	OR‡	95% CI
Nondrinker	9/67	1.0		6/54	0.4	0.1, 1.3	4/18	0.8	0.2, 3.2	3/4	2.7	0.5, 15.8
>0–<8	7/11	4.0	1.1, 14.6	11/75	0.5	0.2, 1.4	18/52	1.7	0.6, 4.4	4/3	2.6	0.5, 15.4
8–<43	9/6	3.5	0.9, 13.8	16/30	1.7	0.6, 4.7	48/38	3.4	1.4, 8.5	15/10	3.9	1.2, 12.6
≥43	17/8	4.9	1.4, 17.4	28/3	8.4	4.2, 79.7	53/13	10.9	3.9, 30.3	29/4	19.1	4.9, 75.2

* Numbers of cases/controls; total = 9/67 nondrinkers, 13/76 drinkers of beer/wine only, 33/25 drinkers of liquor only.
† OR, odds ratio; CI, confidence interval.
‡ Adjusted for age, tobacco use, consumption of raw fruits and vegetables, and educational level.

TABLE 3. Oral cancer risks associated with consumption of types of alcoholic beverages, Puerto Rico, 1992–1995

	No.		Median* no. of drinks/week		OR†,‡	95% CI†	OR§	95% CI
	Cases	Controls	Cases	Controls				
All drinkers (drinks/week)	*n* = 286	*n* = 417						
Beer								
Nondrinker	47	100	23	0	1.0		1.0	
>0–<8	70	170	51	5	0.5	0.3, 1.0	0.5	0.2, 1.0
8–<43	119	121	59	28	1.1	0.6, 2.0	0.6	0.3, 1.3
≥43	42	17	108	69	1.8	0.8, 4.1	0.5	0.2, 1.3
					p-trend = 0.004		*p*-trend = 0.7	
Wine								
Nondrinker	194	317	50	6	1.0		1.0	
>0–<8	62	83	80	11	1.0	0.6, 1.7	0.9	0.6, 1.6
≥8	27	12	165	59	1.8	0.8, 4.3	1.3	0.6, 3.0
					p-trend = 0.2		*p*-trend = 0.5	
Liquor								
Nondrinker	22	147	3	0	1.0		1.0	
>0–<8	40	142	13	8	1.7	0.9, 3.2	1.7	0.8, 3.5
8–<43	90	84	39	29	3.5	1.8, 6.7	2.7	1.2, 6.2
≥43	128	31	119	94	13.2	6.5, 26.6	6.4	2.4, 16.8
					p-trend < 0.0001		*p*-trend = 0.0004	
All liquor drinkers (drinks/week)	*n* = 263	*n* = 270						
Homemade rum								
Nondrinker	49	81	47	9	1.0		1.0	
>0–< 8	146	151	61	15	1.1	0.7, 1.9	1.2	0.7, 2.0
8–<43	30	22	69	52	1.5	0.7, 3.4	1.2	0.5, 2.6
≥43	31	8	172	153	4.5	1.6, 12.5	1.6	0.6, 4.6
					p-trend = 0.004		*p*-trend = 0.5	
Nonhomemade rum liquor								
Nondrinker	37	50	93	11	1.0		1.0	
>0–8	39	128	14	9	0.9	0.4, 1.7	0.9	0.5, 1.9
8–<43	82	71	43	30	1.7	0.9, 3.2	1.3	0.7, 2.5
≥43	103	19	113	84	6.9	3.3, 14.6	3.5	1.6, 7.8
					p-trend < 0.0001		*p*-trend = 0.0005	

* Total alcohol intake.
† OR, odds ratio; CI, confidence interval.
‡ Adjusted for age, tobacco use, consumption of raw fruits and vegetables, educational level, and intake of other alcoholic beverages.
§ Adjusted for age, tobacco use, consumption of raw fruits and vegetables, educational level, and total alcohol intake.

TABLE 4. Oral cancer risks associated with consumption of diluted and undiluted forms of liquor by liquor drinkers, Puerto Rico, 1992–1995

	Usually drank liquor with nonalcoholic mixers				Usually drank liquor straight (undiluted)			
	No.*	Median†	OR‡,§	95% CI‡	No.	Median	OR§	95% CI
All liquor drinkers	57/163		1.0		206/107		4.0	2.4, 6.7
				$p < 0.0001$				
Drinks/week								
>0–<8	19/102	14/8	1.0		21/40	13/9	3.2	1.4, 7.2
8–<22	8/23	23/24	1.0	0.3, 3.0	28/27	24/23	4.2	1.7, 10.5
22–<43	14/13	55/43	3.6	1.2, 10.8	40/18	45/40	7.9	3.0, 21.3
43–<64	8/4	80/74	6.2	1.2, 31.1	27/9	86/63	8.3	2.3, 29.4
64–<137	5/6	113/123	1.1	0.2, 5.4	57/8	121/108	23.5	6.8, 81.5
≥137¶	2/0	204/			29/4	247/450	24.1	5.5, 105.8

* Numbers of cases/controls.
† Total alcohol intake (drinks per week) for cases/controls.
‡ OR, odds ratio; CI, confidence interval.
§ Adjusted for age, tobacco use, consumption of raw fruits and vegetables, educational level, and total alcohol intake.
¶ Extreme values (>450 drinks/week; five cases and three controls) were assigned to 450 drinks/week to calculate median intake.

remained strong across categories of potential confounders; for example, odds ratios were about 4.0 for young (aged 21–64 years) and old (aged 65–79 years) subjects and for subjects whose levels of education were high (≥8 years) and low (<8 years) (data not shown). When liquor consumption was considered as a continuous variable, risks increased per 20 drinks per week; odds ratios were 1.6 (95 percent CI: 1.3, 2.0) for straight-alcohol drinkers and 1.2 (95 percent CI: 0.9, 1.6) for mixed-alcohol drinkers over a comparable dose range (≤136 drinks per week), with evidence of relatively parallel dose-response relations (p for the interaction term = 0.2).

Although numbers were small for evaluating tobacco-alcohol relations by alcohol type, table 5 shows that the

TABLE 5. Oral cancer risks associated with alcohol consumption and tobacco use,* Puerto Rico, 1992–1995

	No–light tobacco use			Medium–heavy tobacco use		
	No.†	OR‡,§	95% CI‡	No.	OR§	95% CI
Beer/wine (drinks/week)						
Nondrinker	13/76	1.0		28/16	3.0	1.0, 8.7
>0–<8	9/101	0.3	0.1, 0.9	52/65	1.7	0.6, 4.8
8–<43	24/83	0.4	0.1, 1.1	99/44	2.1	0.7, 6.1
≥43	7/6	0.6	0.1, 2.8	45/15	1.6	0.5, 5.3
Liquor (drinks/week)						
Nondrinker	10/110	1.0		12/35	4.4	1.5, 12.9
Usually drank liquor with nonalcoholic mixers						
>0–<8	9/68	1.5	0.5, 5.3	10/33	3.4	1.0, 11.4
8–<43	1/21	0.3	0.0, 3.4	21/18	8.4	2.4, 30.2
≥43	1/4	0.8	0.1, 11.4	14/6	9.6	1.8, 50.4
Nondrinker	10/110	1.0		12/35	3.7	1.3, 10.6
Usually drank liquor straight (undiluted)						
>0–<8	6/26	2.7	0.7, 10.5	15/14	13.6	3.9, 47.8
8–<43	13/21	4.9	1.3, 18.8	55/24	15.3	4.5, 51.9
≥43	13/10	8.1	1.7, 38.5	97/11	47.6	11.7, 193.0

* The four categories are defined in the Interview portion of the Materials and Methods section of the text.
† Numbers of cases/controls.
‡ OR, odds ratio; CI, confidence interval.
§ Adjusted for age, consumption of raw fruits and vegetables, educational level, and total alcohol intake.

greatest risks were found among heavy smokers who drank straight liquor. Risks were also elevated for nonsmokers/light smokers who drank straight liquor and for heavy smokers who consumed mixed drinks. Mixed-drink intake did not appear to contribute to risk among subjects whose exposure to tobacco was low, and risks associated with medium-to-heavy tobacco use were unaffected by beer/wine consumption.

DISCUSSION

In this population-based, case-control study of oral cancer in Puerto Rico, we found that risks were more pronounced when equivalent quantities of alcohol were consumed as liquor versus beer/wine, particularly because of consumption of straight versus mixed liquor. We previously reported (1) that oral cancer risks in Puerto Rico increased with increasing exposure to tobacco and alcohol; in the present study, we showed that risks associated with the combined exposures were most apparent among liquor drinkers who usually drank liquor straight. Furthermore, we found no greater risk for homemade rum than for other types of liquor. Our results show that oral cancer risk in Puerto Rico is chiefly attributable to liquor consumed straight, suggesting that alcohol concentration per se is an important risk factor for oral cancer independent of the total quantity of alcohol consumed. That concentration may play a role in carcinogenesis at other sites of direct alcohol exposure is supported by observations from a mainland US study of increased risk for esophageal cancer associated with straight liquor (13).

In the United States (4, 5) and Denmark (6), similar quantities of liquor and beer consumption were related to similar oral cancer risks; in Italy, the greatest risks were associated with wine consumption (9, 10). These studies did not evaluate liquor beverage type (straight vs. mixed). Other analytical limitations in some studies, such as incomplete adjustment for one type of alcohol when assessing the effects of another and limited range of intake of the locally less common beverage types also make beverage-specific comparisons difficult across studies.

Straight-liquor intake is reported more commonly among men in Puerto Rico (controls, 41 percent; 1992–1995) than in the United States (White controls, 18 percent; Black controls, 25 percent; 1986–1989 (13). We did not have comparative data on the frequency and quantity of straight-liquor consumption in other countries. Recent studies from Uruguay (7) and Brazil (8) showed greatest oral cancer risks among consumers of *cachaca* and *caña.* Although these studies also did not specifically investigate the manner of consumption, heavy drinkers usually consume these liquor types straight.

We collected alcohol intake data on a per-drink basis, assuming a standard alcohol equivalence per drink consumed irrespective of beverage type. If there were systematic differentials in portion size by beverage type, then our beverage-type-specific risk estimates may have been biased. For example, liquor volume per drink may differ for consumers of straight versus mixed drinks. We find it unlikely, after adjusting for total alcohol intake, that the observed fourfold differential in risk for habitual straight- versus mixed-liquor drinkers could be due to a differential interpretation by respondents of what constitutes a per-drink portion size. Our categorization of straight- versus mixed-liquor consumption was relatively crude, and confirmation in studies with more specific quantification of alcohol intake by beverage type is warranted. Furthermore, note that the risk estimates in many subgroup analyses, although statistically significant, were rather imprecise and that confidence intervals were wide. Larger studies are needed to enable detailed evaluation of these observations.

In our study, the differential risks associated with alcohol concentration suggest that the carcinogenic effects of alcohol on the oral cavity are primarily local rather than systemic, consistent with the risks to other upper aerodigestive tract tissues that come in contact with alcohol (14). Although the precise mechanism of alcohol-related cancer is unclear, evidence exists that alcohol is converted to a carcinogenic metabolite, acetaldehyde, by bacterial flora in the oral cavity (15, 16) perhaps by enzymes such as alcohol dehydrogenases (17–19). Our study found the highest risks for heavy smokers who drank liquor straight. Highly concentrated alcohol may alter the integrity and permeability of the oral mucosa, enhancing penetration of acetaldehyde, tobacco combustion products, and other potential carcinogens (20–23).

Besides ethanol, congeners and contaminants of alcoholic beverages may also play a role in oral cancer (2). Our observation in Puerto Rico of similar risks for homemade rum and other types of liquor, the findings of similar risks for dark and light liquor in a US mainland study (24), and strong risks for wine consumption observed in Italy (9, 10) argue against an important role of nonethanol ingredients of alcoholic beverages in oral carcinogenesis.

Our population-based, case-control study in Puerto Rico revealed higher risks for consumption of straight versus more dilute alcoholic beverages. Furthermore, alcohol-tobacco interrelations were most apparent among straight-liquor drinkers. The risks of drinking homemade rum were similar to those for other forms of liquor. In summary, our study indicates that consumption of straight liquor is an independent risk factor for oral cancer.

ACKNOWLEDGMENTS

The authors thank Dr. Thomas R. Fears of the National Cancer Institute for statistical advice; Roy van Dusen and Lonn Irish of Information Management Systems, Inc. (Silver Spring, Maryland) for statistical assistance; and the many study coordinators, interviewers, and support staff for their diligent work.

REFERENCES

1. Hayes RB, Bravo-Otero E, Kleinman DV, et al. Tobacco and alcohol use and oral cancer in Puerto Rico. Cancer Causes Control 1999;10:27–33.
2. Alcohol drinking. IARC monographs on the evaluation of car-

cinogenic risks to humans. Vol 44. Lyon, France: International Agency for Research on Cancer, 1988.
3. Blot WJ. Invited commentary: more evidence of increased risks of cancer among alcohol drinkers. Am J Epidemiol 1999;150: 1138–40. (Discussion in Am J Epidemiol 1999;150:1141).
4. Blot WJ, McLaughlin JK, Winn DM, et al. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res 1988; 48:3282–7.
5. Kabat GC, Wynder EL. Type of alcoholic beverage and oral cancer. Int J Cancer 1989;43:190–4.
6. Gronbaek M, Becker U, Johansen D, et al. Population based cohort study of the association between alcohol intake and cancer of the upper digestive tract. BMJ 1998;317:844–7.
7. De Stefani E, Boffetta P, Oreggia F, et al. Hard liquor drinking is associated with higher risk of cancer of the oral cavity and pharynx than wine drinking. A case-control study in Uruguay. Oral Oncol 1998;34:99–104.
8. Schlecht NF, Pintos J, Kowalski LP, et al. Effect of type of alcoholic beverage on the risks of upper aerodigestive tract cancers in Brazil. Cancer Causes Control 2001;12:579–87.
9. Barra S, Franceschi S, Negri E, et al. Type of alcoholic beverage and cancer of the oral cavity, pharynx and esophagus in an Italian area with high wine consumption. Int J Cancer 1990;46: 1017–20.
10. Fioretti F, Bosetti C, Tavani A, et al. Risk factors for oral and pharyngeal cancer in never smokers. Oral Oncol 1999;35:375–8.
11. Martinez I. Factors associated with cancer of the esophagus, mouth, and pharynx in Puerto Rico. J Natl Cancer Inst 1969;42: 1069–94.
12. Breslow NE, Day NE, eds. Statistical methods in cancer research. Vol 1. The analysis of case-control studies. Lyon, France: International Agency for Research on Cancer, 1980. (IARC scientific publication no. 32).
13. Brown LM, Hoover R, Gridley G, et al. Drinking practices and risk of squamous-cell esophageal cancer among Black and White men in the United States. Cancer Causes Control 1997;8: 605–9.
14. Boffetta P, Mashberg A, Winkelmann R, et al. Carcinogenic effect of tobacco smoking and alcohol drinking on anatomic sites of the oral cavity and oropharynx. Int J Cancer 1992;52: 530–3.
15. Homann N, Karkkainen P, Koivisto T, et al. Effects of acetaldehyde on cell regeneration and differentiation of the upper gastrointestinal tract mucosa. J Natl Cancer Inst 1997;89:1692–7.
16. Jokelainen K, Heikkonen E, Roine R, et al. Increased acetaldehyde production by mouthwashings from patients with oral cavity, laryngeal, or pharyngeal cancer. Alcohol Clin Exp Res 1996;20:1206–10.
17. Harty LC, Caporaso NE, Hayes RB, et al. Alcohol dehydrogenase 3 genotype and risk of oral cavity and pharyngeal cancers. J Natl Cancer Inst 1997;89:1698–705.
18. Bosron WF, Li TK. Genetic polymorphism of human liver alcohol and aldehyde dehydrogenases, and their relationship to alcohol metabolism and alcoholism. Hepatology 1986;6:502–10.
19. Schwartz SM, Doody DR, Fitzgibbons ED, et al. Oral squamous cell cancer risk in relation to alcohol consumption and alcohol dehydrogenase-3 genotypes. Cancer Epidemiol Biomarkers Prev 2001;10:1137–44.
20. Muller P, Hepke B, Meldau U, et al. Tissue damage in the rabbit oral mucosa by acute and chronic direct toxic action of different alcohol concentrations. Exp Pathol 1983;24:171–81.
21. Simanowski UA, Suter P, Stickel F, et al. Esophageal epithelial hyperproliferation following long-term alcohol consumption in rats: effects of age and salivary gland function. J Natl Cancer Inst 1993;85:2030–3.
22. Du X, Squier CA, Kremer MJ, et al. Penetration of N-nitrosonornicotine (NNN) across oral mucosa in the presence of ethanol and nicotine. J Oral Pathol Med 2000;29:80–5.
23. Howie NM, Trigkas TK, Cruchley AT, et al. Short-term exposure to alcohol increases the permeability of human oral mucosa. Oral Dis 2001;7:349–54.
24. Day GL, Blot WJ, McLaughlin JK, et al. Carcinogenic risk of dark vs light liquor. Int J Cancer 1994;59:319–21.